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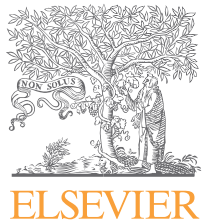

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The EORTC Breast Cancer Group: major achievements of 50 years of research and future directions

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ABSTRACT

The EORTC Breast Cancer Group (BCG), created in 1962, is a multidisciplinary group involving surgeons, medical oncologists, radiation oncologists, pathologists, basic scientists, and clinical research fellows. Currently, more than 80 member's institutions across Europe are participating in the group studies. The main goal of the BCG is to conduct high-quality international clinical trials covering all areas of breast cancer care: from loco-regional to systemic disease control, and from *in situ* carcinoma to metastatic disease. Over 50 years, the BCG has performed dozens of clinical studies including several thousands of patients. Many practice-changing trials and major achievements were conducted optimizing local control, improving systemic therapy in early and metastatic breast cancer, pioneering work in clinical–translational trials and collaboration within intergroup trials. The strategic plan of the BCG for future research includes three distinct albeit overlapping areas: loco-regional therapy, (neo-)adjuvant systemic therapy, trials in the metastatic setting, and niche population studies. For each of these areas the group has considered the prevailing EORTC strategy of focusing on practice-changing studies and translational research, with an emphasis on niche trials. During five decades, the BCG has successfully

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performed a series of practice-changing trials enrolling several thousands of patients. These studies have contributed to the clinical knowledge on the treatment of breast cancer and have influenced clinical practice and breast cancer patients' outcome worldwide.

1. Introduction

The European Organization for Research and Treatment of Cancer (EORTC) Breast Cancer Group (BCG) was created in 1962 as part of the establishment of the EORTC by cancer specialists (including surgical, medical, and radiation oncologists) across Europe with the aim to perform international clinical research in breast cancer. The history and activities of the BCG from 1962 to 2002 have been described previously. [1–3]

Today, the BCG is a multidisciplinary group involving surgeons, medical oncologists, radiation oncologists, pathologists, basic scientists, and clinical research fellows. The main goal of the BCG is to conduct high-quality international clinical trials covering all areas of breast cancer care: from loco-regional to systemic disease control, and from *in situ* carcinoma to metastatic disease. The group actively investigates new anticancer agents in phase I/II trials, and new therapeutic strategies in large phase III trials applying the newest diagnostic modalities, including imaging, sentinel node assessment, histopathology and molecular biology. During the last decade translational research with incorporation of tissue banking has become a top priority of BCG.

Every two years, the BCG organizes the 'European Breast Cancer Conference' (EBCC) in collaboration with the European Society of Breast Cancer Specialists (EUSOMA) and Europa Donna, the European Breast Cancer Coalition. The eighth EBCC will be held in Vienna in March 2012 continuing the tradition of previous conferences by providing excellent opportunities for dialogue between clinicians, researchers, nurses, and patient advocates. The aim of these meetings is to create a platform for closer cooperation between the parties in order both to stimulate scientific progress and to provide better standards of care for breast cancer in Europe and beyond.

2. Summary of BCG achievements during the first 40 years, 1962–2002[A]

Between 1962 and 1973, the activities of the BCG were mostly focused on endocrine therapy in advanced disease. The group was the first to demonstrate the antineoplastic activity of an anti-estrogen, nafoxidine, which was found to be as effective as ethinyloestradiol in postmenopausal women. Nafoxidine was later replaced by a less toxic analogue, tamoxifen. By 1974, a combination of tamoxifen and two alternating regimens of chemotherapy, AV (doxorubicin plus vincristine) and CMF (cyclophosphamide, methotrexate and fluorouracil) were tested by the group. [4] The achievement of high response and complete remission rates stimulated the group to pursue investigations in the field of combined and sequential endocrine therapy and chemotherapy.

In the 1980's, the BCG performed one of the largest studies (EORTC 10801) comparing mastectomy with breast-conserving therapy (BCT) in operable breast cancer, showing that while mastectomy provided slightly better local control, it did not translate into survival advantage. [5,6] This and other practice-changing studies initiated in the 1980–90's continued to accrue long-term follow-up data and resulted in several publications in the last decades of the 20th century, as described below.

In locally advanced disease, the EORTC 10972 trial demonstrated that either endocrine treatment or chemotherapy in addition to radiotherapy significantly delayed the time to first progression, with the greatest effect being achieved with the combination of both (given concomitantly). For overall survival (OS), endocrine treatment and combination of both showed an improvement, whereas chemotherapy did not. [7,8] Between 1986 and 1991, 2795 patients were included in EORTC trial 10854 that showed improved local control with peri-operative chemotherapy, particularly in young women managed with BCT. [9]

Finally, in metastatic disease, the BCG demonstrated that 'classical' CMF is superior to a 3-weekly intravenous CMF schedule in postmenopausal patients (EORTC 10808). [10] In the EORTC 10881 study, the combination of tamoxifen and a luteinizing hormone-releasing hormone (LHRH) inhibitor was found to be superior to either treatment alone in premenopausal patients with advanced breast cancer. [11] Another study (EORTC 10923) compared the efficacy of paclitaxel and doxorubicin given as single agents in first-line therapy of advanced breast cancer with a planned cross-over applied systematically on progression during first-line treatment. This trial demonstrated that doxorubicin provides better disease control (objective response and progression-free survival [PFS]) and symptom control (particularly pain) than paclitaxel

[A] A detailed description has been published previously. [1–3]

as first-line treatment. No significant survival difference was observed between the two treatment groups. This trial additionally identified non cross-resistance between doxorubicin and paclitaxel irrespective of what sequence these drugs are administered. [12]

3. Major achievements in the last decade

Over the last three years the BCG has recruited a total of over 4000 patients from 57 medical centers into clinical trials, an average of 1340 patients per year. These patients have been included not only in EORTC studies but also in intergroup trials in which the EORTC is one of the partners. High-quality data are ensured by standardized procedures and fully dedicated personnel including highly qualified statisticians at EORTC Headquarters. In the last few years, most BCG trials have incorporated a central pathology review process of collected tumor samples to assure high-quality and annotated pathology data, which renders possible important translational research activities. As part of quality assurance activities in radiotherapy, a survey among EORTC-radiotherapy centers described precise details of radiotherapy techniques currently implemented for breast irradiation in Europe and showed that recent advances in radiotherapy technology are being widely adopted. [13] It indicates that new radiotherapy techniques, when being addressed in clinical trials, are feasible within the network of EORTC-ROG centers.

4. Optimizing local control

4.1. *Breast-conserving surgery followed by radiotherapy (RT) has equivalent long-term efficacy to mastectomy*

In the 1980's, some studies showed that BCT, if followed by RT, was as effective as mastectomy in the treatment of breast tumors of 2 cm or smaller. However, evidence of its long-term efficacy, in patients with tumors larger than 2 cm, was at that time limited. The EORTC 10801 study, run between 1980 and 1986, was one of the largest randomized trials (n = 868) to compare BCT followed by RT with modified radical mastectomy for patients with operable breast cancer up to 5 cm. Eighty percent of the patients had a tumor of 2.1–5 cm and 40% positive lymph nodes. At a median follow-up of 13 years, patients assigned to BCT had a higher risk of loco-regional recurrence (HR = 1.64, 95% CI: 1.12–2.38; $P = 0.01$) than the mastectomy group, however there was no difference in OS (HR = 1.13, 95% CI: 0.92–1.39; $P = 0.246$). [14] An update analysis with 22 years follow-up has been conducted and will be available soon.

4.2. *Addition of boost radiation after BCT improves local control*

In collaboration with the EORTC Radiotherapy Group the EORTC 22881–10882 trial recruited more than 5000 patients with stage I/II breast cancer treated with BCT and whole breast irradiation. The study demonstrated that an additional boost dose of radiation to the tumor bed reduces the risk of local recurrence (7.3% *versus* 4.3%; HR = 0.59; $P < 0.001$), particularly in patients below than 50 years of age. [15] The later analysis, with a median follow-up of 10.8 years, demonstrated that a boost dose of 16 Gy improved local control in all age groups (10-year local recurrence of 10.2% vs. 6.2%; HR = 0.59; $P < 0.0001$ in favor of boost), but without a difference in OS. [16]

4.3. *Adjuvant radiotherapy improves local control of DCIS after BCT*

In one of the largest clinical studies ever performed in ductal carcinoma in situ (DCIS) of the breast, the EORTC 10853 trial, the beneficial effect of RT was demonstrated in reducing the overall number of both invasive and non-invasive recurrences in the ipsilateral breast after BCT. [17] With long-term follow-up of ten years, local recurrence-free rate in the groups treated with local excision with and without RT was 85% and 74%, respectively (HR = 0.53; $P < 0.0001$). RT after local excision for DCIS continued to reduce the risk of local recurrence (DCIS and invasive disease), with a 47% reduction at ten years. All patient subgroups benefited from RT. [18] A further analysis on a longer follow-up is planned in the near future.

The BCG also demonstrated in a prospective study (EORTC 10873) that BCT is a feasible alternative for patients with Paget disease, a rare type of breast cancer, and a limited extent of underlying DCIS. To achieve good local control, treatment should include a complete excision of the nipple areolar complex including the underlying disease, followed by irradiation to the whole breast. [19]

5. Improved systemic therapy in early and metastatic breast cancer

5.1. *Neoadjuvant and adjuvant treatment are equivalent in terms of breast cancer outcome*

The hypothesis that preoperative systemic treatment might be more effective than classical adjuvant treatment was investigated in a phase III trial (EORTC 10902). This study confirmed that both strategies yield similar results in terms of PFS, OS, and locoregional control. [20] In the same setting, another phase III study (EORTC 10921) showed no benefit of intensified induction chemotherapy with granulocyte colony stimulating factor (GCSF) support, compared with standard chemotherapy. [21]

5.2. Standard anthracycline-based chemotherapy remains a reasonable treatment choice as first-line chemotherapy for metastatic breast cancer patients not previously treated with this class of agents

The BCG also performed a phase III trial (EORTC 10961) to compare the efficacy and tolerability of the combination of doxorubicin and paclitaxel (AT) with a standard doxorubicin plus cyclophosphamide (AC) regimen as first-line chemotherapy for metastatic breast cancer. No differences in PFS, being six months in both the treatment arms ($P = 0.65$), or OS (20.6 *versus* 20.5 months; $P = 0.49$) were observed between the two treatment arms. The AT regimen was accompanied by a higher incidence of toxicity which compromised doxorubicin-delivered dose-intensity in this arm. [22] In a later meta-analysis, which included the results of this trial, taxane-based combinations were found to be better than anthracycline-based combinations in terms of response rates (HR = 0.63, 95% CI: 0.54–0.72; $P = 0.001$) and PFS (HR = 0.92, 95% CI: 0.85–0.99; $P = 0.031$) but not in terms of OS (HR = 0.95, 95% CI: 0.88–1.03; $P = 0.24$). [23]

6. Pioneering work in clinical-translational trials

During the last decade pioneering work in breast cancer translational research and biobanking has been led by BCG in collaboration with other EORTC groups and other international partners. Based on the current BCG experience, high-quality clinical trials with a strong translational research component and/or answering a molecular biology-based primary question are feasible in a multicenter and multinational setting in Europe.

The "*p53* trial" (EORTC 10994 BIG 1-00), one of the first international trials with a molecular-based question as primary endpoint, did not confirm its primary hypothesis that a somatic *p53* mutation conferred additional benefit to taxanes over anthracyclines. However, the prognostic value of p53 alterations in early breast cancer was confirmed. Importantly, enrolment in this trial demanded the availability of a snap-frozen core biopsy from each patient, making this enterprise one of the largest neoadjuvant breast cancer trials ever done with collection of fresh-frozen tumor samples from all enrolled patients. [24] Using this valuable material two important translational research projects have been performed and published in high-profile journals: the identification of molecular apocrine breast tumors by microarray analysis, and a stroma-related gene signature which predicts resistance to neoadjuvant chemotherapy in breast cancer. [25,26]

The EORTC 10041 BIG 3-04 MINDACT (Microarray In Node-negative and one to three positive lymph node Disease may Avoid ChemoTherapy) is a phase III trial evaluating the clinical utility and added clinical benefit of the 70-gene genomic signature (MammaPrint™) to traditional clinical-pathological methods for selecting early breast cancer patients for adjuvant chemotherapy. MINDACT, together with TailorX run in the USA, is the first clinical trial evaluating the clinical utility of a multigene tool. It is also the first trial to collect frozen tumor samples and run gene expression profiling on a real-time basis (results provided within a maximum of ten days) and in a multinational, multicenter setting. The results of the MINDACT pre-planned pilot phase which included the first 800 patients were presented at the EBCC7 in 2010 and ECCO in 2011. [27,28] The main conclusions were that this logistically complex trial is feasible in a multinational multicenter setting, and that the proportion of discordant patients, the estimated reduction of chemotherapy prescription by using the 70-gene profile, and the compliance to treatment assignment in the discordant group were all according to plan. The trial completed the planned accrual of 6600 patients in July 2011. This landmark trial collected fresh-frozen tumor samples, paraffin tissue blocks and blood/serum samples from all enrolled patients for current and future translational research This valuable annotated high-quality biological material is stored in an independent biobank and available to the scientific community according to a specific policy (available at www.breastinternationalgroup.org).

7. Collaboration within intergroup trials

With the identification of specific molecular subtypes of breast cancer, international collaboration between different cooperative groups has become indispensible to achieve further improvements in the management of breast cancer, especially in the area of systemic therapy for early breast cancer. Intergroup collaboration avoids duplication of efforts and wasting of resources and allows the recruitment of the necessary numbers of patients of each molecular subtype. The EORTC is one of the founding organizations of the Breast International Group (BIG), a worldwide network of 44 breast cancer research groups from 40 countries, founded in 1996 by Martine Piccart (former EORTC President and BCG Chair) and Aron Goldhirsch. Over the past 15 years, BIG has formed a powerful platform for clinical and translational collaboration and successfully performed landmark and practice changing trials. The BCG has actively participated in and coordinated some of these important international, intergroup studies, enrolling more than 5500 patients; most important of these studies are "p53 trial", MINDACT, HERA, ALTTO, MA17, IES and SOFT.

The Herceptin Adjuvant (HERA) trial (BIG 0101) was one of several large trials designed to test the efficacy of trastuzumab in the adjuvant treatment of women with

HER-2 over-expressing and/or amplified operable breast cancer. The results showed that one year treatment with adjuvant trastuzumab after completion of chemotherapy and radiotherapy is associated with significant clinical benefit compared to observation (4-year disease-free survival [DFS] 78.6% vs. 72.2%).[29] In the same field, the BCG has joined the ALTTO trial (Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization), which recruited more than 8000 patients, to test the hypothesis that combining or sequencing two anti-HER-2 targeted agents in the adjuvant treatment of patients with HER-2-positive breast cancer confers additional benefit over one year of trastuzumab alone.

In addition, the BCG participated in two important trials of adjuvant endocrine therapy for early breast cancer. The MA.17 study included 5187 postmenopausal women to investigate the extended adjuvant therapy with the aromatase inhibitor letrozole after five years of tamoxifen.[30] The results showed that five years of letrozole after tamoxifen reduces the risk of late recurrences, improves DFS and distant disease-free survival (DDFS) but not OS. The Intergroup Exemestane Study (IES) enrolled 4742 patients to investigate whether exemestane, when given to postmenopausal women who remained free of recurrence after receiving adjuvant tamoxifen therapy for two to three years for primary breast cancer, could prolong disease DFS, as compared with continued tamoxifen therapy for a total of five years. Exemestane led to a 24% reduction in risk of recurrence corresponding to an absolute benefit of 3.3% by the end of treatment (i.e., 2.5 years after randomization). This strategy also reduced the risk of contralateral breast cancer, endometrial cancer and other primary cancers. OS was not significantly different between the two groups.[31,32]

8. Future directions

The strategic plan of the BCG for future research includes three distinct albeit overlapping areas: loco-regional therapy, (neo-)adjuvant systemic therapy, trials in the metastatic setting, and niche studies (such as male breast cancer). For each of these areas the group has considered the prevailing EORTC strategy of focusing on practice changing studies and translational research, with an emphasis on niche trials. The following are examples of this work.

8.1. Loco-regional therapy

The EORTC 10981–22023 AMAROS (After Mapping of the Axilla: Radiotherapy Or Surgery) study is a phase III trial with the objective to prove equivalent local/regional control between axillary lymph node dissection (ALND) and axilla radiotherapy (ART) in sentinel node (SN) positive early BC patients. The trial achieved the planned accrual in April 2010. First interim analysis showed a high identification rate of SN (97%), 34% of the SN's containing metastases.[33] Further, patterns of care analysis revealed that the lack of knowledge of the axillary nodal status in SN positive patients does not influence the type or dose of adjuvant chemotherapy.[34] A follow-up trial, continuing to optimize the loco-regional management of early breast cancer, is being developed.

Furthermore BCG centers participate in a worldwide trial to assess the optimal radiation dose and fractionation schedule for DCIS (EORTC 22085–10083).

8.2. (Neo-)adjuvant systemic therapy studies

The refinement of targeted therapy against HER-2 is being assessed in the EORTC 10054 trial (Lapatax). This is a phase I–II trial designed to compare the use of lapatinib, trastuzumab or lapatinib plus trastuzumab in combination with docetaxel after FEC as neoadjuvant chemotherapy for operable and locally advanced breast cancer. The trial will enroll 150 patients from European centers and will collect frozen tumor and blood samples for translational research.

The BCG will continue to explore the neo-adjuvant setting as a means of speeding up drug development for specific molecular subtypes of early breast cancer associated with important translational research projects. Due to inherent recruitment challenges, these studies will most likely be performed within the EORTC Network of Core Institutions (NOCI) and/or within the recently created international network neo-BIG.

8.3. Niche studies

Breast cancer in specific populations such as male, elderly or very young patients are also areas of great interest that must be explored by academic groups.

The BCG is currently coordinating a worldwide collaboration (including BIG and the North American Breast Cancer Groups [NABCG] networks) aiming to obtain a better clinical and biological characterization of male breast cancer (EORTC 10085 BIG2-07 trial). This is an international joint program with three planned parts:

(a) a retrospective joint analysis of the largest series of male breast cancer cases in terms of clinical and biological (centrally accessed) characteristics;
(b) a prospective registry of all male breast cases treated within this large international network within a period of two years;
(c) depending on the results of the previous parts, a prospective randomized clinical trial of adjuvant endocrine therapy.

It is important to emphasize that all previous efforts to run randomized trials in this patient population have failed and that only this large, worldwide collaboration may render it possible to achieve.

The BCG will continue to collaborate with the EORTC Elderly Task Force in its efforts to develop trials of new therapies/strategies for this ever increasing and quite specific patient population.

As in the early setting, breast cancer in the metastatic setting must also be studied separately according to different molecular subtypes with foreseeable consequences for patient accrual. A variety of new agents are already in development, and their number will likely further increase in the next few years. Only through well organized international collaboration will advances in this area be achieved. The BCG will increase its focus on the metastatic setting and take the lead in several of these projects.

9. Conclusions

The BCG has been successful in its mission to carry out large clinical studies covering the entire spectrum of breast tumors from intraductal carcinoma to metastatic disease. These studies have focused on optimization of local and systemic therapy of breast cancer and have also considered quality of life and health economics. Over five decades, the BCG has successfully performed a series of practice-changing trials and has enrolled several thousand patients. These studies have contributed to the clinical knowledge on the treatment of breast cancer and have influenced clinical research and clinical practice worldwide.

In this new era of molecular-based medicine, the BCG is prioritizing translational research, biobanking, quality assurance issues, and trials in specific populations. Together with the increasing participation of young oncologists and active lobbying for independent and centralized European funding resources, these activities will certainly maintain the status of the BCG as a world renowned leading player in clinical breast cancer research.

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11. Conflict of interest statement

Gustavo Werutsky, Sandrine Marreaud, Jan Bogaerts, Etienne Brain, Lissandra Dal Lago, Fatima Cardoso, Helen Westenberg, Suzette Delaloge, Emiel Rutgers, Jacek Jassem, Luigi Cataliotti, Laura Van't Veer, Tanja Cufer, Herve Bonnefoi, and Geertjan van Tienhoven declare no conflicts of interest. David Cameron consulted for and his institution received honoraria and research funds from Roche.

References

1. Wildiers J, Vantongelen K, van Dongen JA, Rotmensz N, Sylvester R. Activities of the EORTC Breast Cancer Co-operative Group: an overview. [European Organization for Research and Treatment of Cancer]. *Eur J Cancer Clin Oncol* 1988;**24**:3–8.
2. Paridaens R, Mattheiem WH, van Dongen JA, et al. An overview of the EORTC Breast Cancer Cooperative Group's activities. *Eur J Cancer Clin Oncol* 1983;**19**:1665–9.
3. Therasse P, Piccart M, van de Velde CJ, Jassem J. The EORTC Breast Cancer Group: 40 years of research contributing to improve breast cancer management. *Eur J Cancer* 2002;**38**(Suppl 4):S39–43.
4. Heuson JC, Sylvester R, Engelsman E. Alternating cyclical hormonal-cytotoxic combination chemotherapy in postmenopausal patients with breast cancer. An EORTC trial. *Eur J Cancer* 1980;Suppl 1:113–7.
5. van Dongen JA, Bartelink H, Fentiman IS, et al. Randomized clinical trial to assess the value of breast conserving therapy in stage I and II breast cancer, EORTC 10801 trial. *J Natl Cancer Inst Monogr* 1992;(11):15–8.
6. van Dongen JA, Bartelink H, Fentiman IS, et al. Factors influencing local relapse and survival and results of salvage treatment after breast-conserving therapy in operable breast cancer: EORTC trial 10801, breast conservation compared with mastectomy in TNM stage I and II breast cancer. *Eur J Cancer* 1992;**28A**:801–5.
7. Bartelink H, Rubens RD, van der Schueren E, Sylvester R. Hormonal therapy prolongs survival in irradiated locally advanced breast cancer: a European Organization for Research and Treatment of Cancer randomized Phase III trial. *J Clin Oncol* 1997;**15**:207–15.
8. Rubens RD, Bartelink H, Engelsman E, et al. Locally advanced breast cancer: the contribution of cytotoxic and endocrine treatment to radiotherapy. An EORTC Breast Cancer Co-operative Group Trial (10792). *Eur J Cancer Clin Oncol* 1989;**25**:667–78.
9. van der Hage JA, van de Velde CJ, Julien JP, et al. Improved survival after one course of perioperative chemotherapy in early breast cancer patients. Long-term results from the European Organization for Research and Treatment of Cancer (EORTC) Trial 10854. *Eur J Cancer* 2001;**37**:2184–93.
10. Engelsman E, Klijn JC, Rubens RD, et al. "Classical" CMF versus a 3-weekly intravenous CMF schedule in postmenopausal patients with advanced breast cancer.

An EORTC Breast Cancer Co-operative Group Phase III Trial (10808). *Eur J Cancer* 1991;**27**:966–70.
11. Klijn JG, Beex LV, Mauriac L, et al. Combined treatment with buserelin and tamoxifen in premenopausal metastatic breast cancer: a randomized study. *J Natl Cancer Inst* 2000;**92**:903–11.
12. Paridaens R, Biganzoli L, Bruning P, et al. Paclitaxel versus doxorubicin as first-line single-agent chemotherapy for metastatic breast cancer: a European Organization for Research and Treatment of Cancer randomized study with cross-over. *J Clin Oncol* 2000;**18**:724–33.
13. van der Laan HP, Hurkmans CW, Kuten A, Westenberg HA. Current technological clinical practice in breast radiotherapy; results of a survey in EORTC-Radiation Oncology Group affiliated institutions. *Radiother Oncol* 2010;**94**:280–5.
14. van Dongen JA, Voogd AC, Fentiman IS, et al. Long-term results of a randomized trial comparing breast-conserving therapy with mastectomy: European Organization for Research and Treatment of Cancer 10801 trial. *J Natl Cancer Inst* 2000;**92**:1143–50.
15. Bartelink H, Horiot JC, Poortmans P, et al. Recurrence rates after treatment of breast cancer with standard radiotherapy with or without additional radiation. *N Engl J Med* 2001;**345**:1378–87.
16. Bartelink H, Horiot JC, Poortmans PM, et al. Impact of a higher radiation dose on local control and survival in breast-conserving therapy of early breast cancer: 10-year results of the randomized boost versus no boost EORTC 22881–10882 trial. *J Clin Oncol* 2007;**25**:3259–65.
17. Julien JP, Bijker N, Fentiman IS, et al. Radiotherapy in breast-conserving treatment for ductal carcinoma in situ: first results of the EORTC randomised phase III trial 10853. EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *Lancet* 2000;**355**:528–33.
18. Bijker N, Meijnen P, Peterse JL, et al. Breast-conserving treatment with or without radiotherapy in ductal carcinoma-in-situ: ten-year results of European Organisation for Research and Treatment of Cancer randomized phase III trial 10853 – a study by the EORTC Breast Cancer Cooperative Group and EORTC Radiotherapy Group. *J Clin Oncol* 2006;**24**:3381–7.
19. Bijker N, Rutgers EJ, Duchateau L, et al. Breast-conserving therapy for Paget disease of the nipple: a prospective European Organization for Research and Treatment of Cancer study of 61 patients. *Cancer* 2001;**91**:472–7.
20. van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. *J Clin Oncol* 2001;**19**:4224–37.
21. Therasse P, Mauriac L, Welnicka-Jaskiewicz M, et al. Final results of a randomized phase III trial comparing cyclophosphamide, epirubicin, and fluorouracil with a dose-intensified epirubicin and cyclophosphamide + filgrastim as neoadjuvant treatment in locally advanced breast cancer: an EORTC–NCIC–SAKK multicenter study. *J Clin Oncol* 2003;**21**:843–50.
22. Biganzoli L, Cufer T, Bruning P, et al. Doxorubicin and paclitaxel versus doxorubicin and cyclophosphamide as first-line chemotherapy in metastatic breast cancer: The European Organization for Research and Treatment of Cancer 10961 multicenter Phase III trial. *J Clin Oncol* 2002;**20**:3114–21.
23. Piccart-Gebhart MJ, Burzykowski T, Buyse M, et al. Taxanes alone or in combination with anthracyclines as first-line therapy of patients with metastatic breast cancer. *J Clin Oncol* 2008;**26**:1980–6.
24. Bonnefoi H, Piccart M, Bogaerts J, et al. TP53 status for prediction of sensitivity to taxane versus non-taxane neoadjuvant chemotherapy in breast cancer (EORTC 10994/BIG 1-00): a randomised phase 3 trial. *Lancet Oncol* 2011;**12**:527–39.
25. Farmer P, Bonnefoi H, Becette V, et al. Identification of molecular apocrine breast tumours by microarray analysis. *Oncogene* 2005;**24**:4660–71.
26. Farmer P, Bonnefoi H, Anderle P, et al. A stroma-related gene signature predicts resistance to neoadjuvant chemotherapy in breast cancer. *Nat Med* 2009;**15**:68–74.
27. Mook S, Bonnefoi H, Pruneri G, et al. Daily clinical practice of fresh tumour tissue freezing and gene expression profiling; logistics pilot study preceding the MINDACT trial. *Eur J Cancer* 2009;**45**:1201–8.
28. Rutgers E, Piccart M, Delaloge S, et al. The EORTC 10041/BIG 03-04 MINDACT trial is feasible: first results of the pilot phase. 7th European Breast Cancer Conference (EBCC-7). *EJC Suppl* 2010;**8**:444.
29. Gianni L, Dafni U, Gelber RD, et al. Treatment with trastuzumab for 1 year after adjuvant chemotherapy in patients with HER2-positive early breast cancer: a 4-year follow-up of a randomised controlled trial. *Lancet Oncol* 2011;**12**:236–44.
30. Goss PE, Ingle JN, Martino S, et al. Randomized trial of letrozole following tamoxifen as extended adjuvant therapy in receptor-positive breast cancer: updated findings from NCIC CTG MA.17. *J Natl Cancer Inst* 2005;**97**:1262–71.
31. Coombes RC, Hall E, Gibson LJ, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. *N Engl J Med* 2004;**350**:1081–92.
32. Coombes RC, Kilburn LS, Snowdon CF, et al. Survival and safety of exemestane versus tamoxifen after 2–3 years' tamoxifen treatment (Intergroup Exemestane Study): a randomised controlled trial. *Lancet* 2007;**369**:559–70.
33. Straver ME, Meijnen P, van Tienhoven G, et al. Sentinel node identification rate and nodal involvement in the EORTC 10981–22023 AMAROS trial. *Ann Surg Oncol* 2010; **17**:1854–61.
34. Straver ME, Meijnen P, van Tienhoven G, et al. Role of axillary clearance after a tumor-positive sentinel node in the administration of adjuvant therapy in early breast cancer. *J Clin Oncol* 2010;**28**:731–7.